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APPLICATION NUMBER: *60/540,307*
FILING DATE: *January 28, 2004*

PRIORITY DOCUMENT
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PTO/SB/16 (08-03)
Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No.

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Additional inventors are being named on the 1 *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

A CRYSTALLINE FORM OF 1-(((1(R)-(3-(2-(7-CHLORO-2-QUINOLINYL)ETHENYL)-PHENYL)-3-(2-(1-HYDROXY-1-METHYLETHYL) PHENYL) PROPYL) THIO) METHYL) CYCLOPROPANE ACETIC ACID

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ENCLOSED APPLICATION PARTS (*check all that apply*)

- [X] Specification *Number of Pages* 16
- [ ] Drawing(s) *Number of Sheets* 3
- [X] Application Data Sheet. See 37 CFR 1.76
- [ ] CD(s), Number
- [ ] Other (specify):

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

- [ ] Applicant claims small entity status. See 37 CFR 1.27.
- [X] A check or money order is enclosed to cover the filing fees.
- [X] The Director is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 04-0100
- [ ] Payment by credit card. Form PTO-2038 is attached.

FILING FEE AMOUNT ($): 160.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

[X] No [ ] Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted, S. Peter Ludwig

Date January 28, 2004

SIGNATURE

TYPED OR PRINTED NAME S. Peter Ludwig, Esq.

REGISTRATION NO. *(if appropriate)* 25,351

TELEPHONE (212) 527-7770

Docket Number: 03818/0200780-US0

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

Express Mail Label No. Dated:

PROVISIONAL APPLICATION COVER SHEET
Additi nal Page

PTO/SB/16 (08-03)
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Docket Number	03818/0200780-US0

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Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 160.00

Complet if Known	
Application Number	Not Yet Assigned
Filing Date	Concurrently Herewith
First Named Inventor	Michaela Horvat
Examiner Name	Not Yet Assigned
Art Unit	N/A
Attorney Docket No.	03818/0200780-US0

METHOD OF PAYMENT *(check all that apply)*

☒ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None

☐ Deposit Account:

Deposit Account Number: 04-0100

Deposit Account Name: Darby & Darby P.C.

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	160.00

SUBTOTAL (1) ($) 160.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

		Extra Claims	Fee from below	Fee Paid
Total Claims	16	-** =	x	=
Independent Claims	3	-** =	x	=
Multiple Dependent				=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0.00

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FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge – late filing fee or oath	
1052	50	2052	25	Surcharge – late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive – unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify)

*Reduced by Basic Filing Fee Paid **SUBTOTAL (3)** ($) 0.00

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Application No. (if known): Attorney Docket No.: 03818/0200780-US0

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Provisional Patent Application Transmittal (2 pages)
Fee Transmittal (1 page)
Application Data Sheet (3 pages)
Specification, Claims and Abstract (16 pages)
3 sheet of drawings (Figs. 1-3)
Check No. 4002 in the amount of $160.00

Application Data She t

Application Information

Application Type::	Provisional
Subject Matter::	Utility
Suggested Group Art Unit::	N/A
CD-ROM or CD-R?::	None
Sequence submission?::	None
Computer Readable Form (CRF)?::	No
Title::	A CRYSTALLINE FORM OF 1-(((1(R)-(3-(2-(7-CHLORO-2-QUINOLINYL)ETHENYL)-PHENYL)-3-(2-(1-HYDROXY-1-METHYLETHYL) PHENYL) PROPYL) THIO) METHYL) CYCLOPROPANE ACETIC ACID
Attorney Docket Number::	03818/0200780-US0
Request for Early Publication?::	No
Request for Non-Publication?::	No
Small Entity?::	No
Petition included?::	No
Secrecy Order in Parent Appl.?::	No

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A CRYSTALLINE FORM OF 1-(((1(*R*)-(3-(2-(7-CHLORO-2-QUINOLINYL)ETHENYL)-PHENYL)-3-(2-(1-HYDROXY-1-METHYLETHYL)PHENYL)PROPYL) THIO)METHYL) CYCLOPROPANE ACETIC ACID

Field of the Invention

The present invention relates to a new crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl) cyclopropane acetic acid, to a process for its preparation, to pharmaceutical formulations containing it, and to a method of treatment using the same.

Background of the Invention

The sodium salt of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropane acetic acid (Montelukast sodium) is a therapeutic agent useful for the treatment of bronchial asthma. Montelukast sodium is disclosed in European Patent Application No. 480,717.

EP 480,717 does not disclose the solid state characterization of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1methylethyl)phenyl)propyl)thio) methyl) cyclopropane acetic acid or the sodium salt thereof.

Summary of the Invention

In one embodiment, the present invention is directed to a new crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl) phenyl)propyl)thio) methyl)cyclopropane acetic acid.

In a second embodiment, the disclosure is directed to a process for the preparation of the new crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio) methyl)cyclopropane acetic acid.

A further embodiment is directed to a pharmaceutical composition containing the new crystalline form, and yet another embodiment is directed to a method of treatment using the new crystalline form.

Brief Description of the Drawings

Figure 1 shows an X-ray powder diffraction pattern (XRPD) of the crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl) phenyl)propyl)thio) methyl)cyclopropane acetic acid of the present invention.

Figure 2 shows an infra-red (IR) spectrum of the crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl) cyclopropane acetic acid of the present invention.

Figure 3 shows a differential scanning calorimetry (DSC) thermogram of the crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl) phenyl)propyl)thio) methyl)cyclopropane acetic acid of the present invention.

Detailed Description of the Invention

A new crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropane acetic acid can be prepared by recrystallization of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropane acetic acid from a mixture of one or more aqueous buffers and acetone.

The starting material used to prepare the new crystalline form may be any amorphous or crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl) phenyl)propyl)thio)methyl)cyclopropane acetic acid, or any salt thereof.

For the recrystallization, the pH range of the aqueous buffer is typically between about 2 and about 8, preferably from about 3 to about 7, and most preferably from about 4 to about 6. The ratio of aqueous buffer to acetone used in the recrystallization is typically from about 1:10 to about 10:1, preferably from about 1:4 to about 4:1, and most preferably from about 1:2 to about 2:1. The recrystallization temperature is typically between about 5 °C and about 50 °C, preferably from about 10 °C to about 40 °C, and most preferably from about 20 °C to about 30 °C.

Suitable aqueous buffers include, but are not limited to, acetate, citric, biphtalate, and phosphate buffers.

A single crystal of the new crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl) cyclopropane acetic acid was prepared, and single crystal X-ray diffraction data collected using a Bruker Nonius FR591/Kappa CCD diffractometer using CuKα radiation. Pertinent crystallographic data thus obtained data are set forth in Table 1.

TABLE 1. Crystallographic data for the new crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl) cyclopropane acetic acid

Chemical formula	$(C_{35}H_{35}ClNO_3S)_2$
Empirical formula weight	585.15
Temperature	293(2) K
Crystal size	0.06 x 0.10 x 0.25 mm
Crystal system, space group	Monoclinic, $P\,2_1$
Unit cell dimension	a = 7.95(1) Å
	b = 21.94(1) Å
	c = 17.95(1) Å
	β= 100.03(1) °
	3082(1) Å^3
1. Z	2
Calculated density	1.26(1) g cm^{-3}

The new crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropane acetic acid has characteristic X-ray powder diffraction peaks (designated by "2θ" and expressed in degrees) as

follows; 6.5±0.2°, 10.0±0.2°, 15.5±0.2°, 18.3±0.2°, 20.4±0.2°, 24.6±0.2°, measured using CuKα radiation on a powder sample collected using a Philips X'PertPRO powder diffractometer. This is shown in Figure 1.

Figures 2 and 3 show the Differential Scanning Calorimetry thermogram (DSC) and Infrared spectrum (IR), respectively, of the new crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl) cyclopropane acetic acid of the present invention. In the IR (Figure 2), characteristic bands are observed at 1715±5 cm^{-1} and 3573±5 cm^{-1}. In the DSC (Figure 3), a characteristic endothermic peak in range from 120 °C to 180 °C is observed.

The purity of the solid new crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl) cyclopropane acetic acid obtained using the process of the present invention is typically greater than about 90.0 %, preferably greater than about 95.0 %, more preferably greater than about 99.0 % and the most preferably greater than about 99.9 %.

Therapeutic Formulations and Regimens

The new crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl) cyclopropane acetic acid of the present invention can be utilized in the preparation of rapid, controlled and sustained release pharmaceutical formulations, suitable for oral, rectal, parenteral, transdermal, buccal,

nasal, sublingual, subcutaneous or intravenous administration. Such formulations may be useful for the treatment of asthma in a human.

The formulations are preferably administered orally, in the form of rapid or controlled release tablets, microparticles, mini tablets, capsules and oral solutions or suspensions, or powders for the preparation thereof. In addition to the new crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio) methyl) cyclopropane acetic acid of the present invention as the active substance, oral preparations may optionally include various standard pharmaceutical carriers and excipients, such as binders, fillers, buffers, lubricants, glidants, disintegrants, odorants, sweeteners, surfactants and coatings. Some excipients may have multiple roles in the formulations, e. g., act as both binders and disintegrants.

Examples of pharmaceutically acceptable disintegrants for oral formulations useful in the present invention include, but are not limited to, starch, pre-gelatinized starch, sodium starch glycolate, sodium carboxymethylcellulose, croscarmellose sodium, microcrystalline cellulose, alginates, resins, surfactants, effervescent compositions, aqueous aluminum silicates and crosslinked polyvinylpyrrolidone.

Examples of pharmaceutically acceptable binders for oral formulations useful herein include, but are not limited to, acacia; cellulose derivatives, such as methylcellulose, carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose or hydroxyethylcellulose; gelatin, glucose, dextrose, xylitol, polymethacrylates, polyvinylpyrrolidone, sorbitol, starch, pre-gelatinized starch, tragacanth, xanthane resin, alginates, magnesium–aluminum silicate, polyethylene glycol or bentonite.

Examples of pharmaceutically acceptable fillers for oral formulations include, but are not limited to, lactose, anhydrolactose, lactose monohydrate, sucrose, dextrose, mannitol, sorbitol, starch, cellulose (particularly microcrystalline cellulose), dihydro- or anhydro-calcium phosphate, calcium carbonate and calcium sulfate.

Examples of pharmaceutically acceptable lubricants useful in the formulations of the invention include, but are not limited to, magnesium stearate, talc, polyethylene glycol, polymers of ethylene oxide, sodium lauryl sulfate, magnesium lauryl sulfate, sodium oleate, sodium stearyl fumarate, DL-leucine and colloidal silicon dioxide

Examples of suitable pharmaceutically acceptable odorants for the oral formulations include, but are not limited to, synthetic aromas and natural aromatic oils such as extracts of oils, flowers, fruits and combinations thereof. Preferable are vanilla and fruit aromas, including banana, apple, sour cherry, peach and similar aromas. Their use depends on many factors, the most important being the organoleptic acceptability for the population that will be taking the pharmaceutical formulations.

Examples of suitable pharmaceutically acceptable dyes for the oral formulations include, but are not limited to, synthetic and natural dyes such as titanium dioxide, beta-carotene and extracts of grapefruit peel.

Examples of useful pharmaceutically acceptable coatings for the oral formulations, typically used to facilitate swallowing, modify the release properties, improve the appearance, and/or mask the taste of the formulations include, but are not limited to, hydroxypropylmethylcellulose, hydroxypropylcellulose and acrylate-methacrylate copolymers.

Suitable examples of pharmaceutically acceptable sweeteners for the oral formulations include, but are not limited to, aspartame, saccharin, saccharin sodium, sodium cyclamate, xylitol, mannitol, sorbitol, lactose and sucrose.

Suitable examples of pharmaceutically acceptable buffers include, but are not limited to, citric acid, sodium citrate, sodium bicarbonate, dibasic sodium phosphate, magnesium oxide, calcium carbonate and magnesium hydroxide.

Suitable examples of pharmaceutically acceptable surfactants include, but are not limited to, sodium lauryl sulfate and polysorbates.

Formulations of the new crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl) cyclopropane acetic acid of the present invention can also be administered intravenously or intraperitoneally, by infusion or injection. Dispersions can also be prepared in a liquid carrier or intermediate, such as glycerin, liquid polyethylene glycols, triacetin oils, and mixtures thereof. To improve storage stability, such preparations may also contain a preservative to prevent the growth of microorganisms.

Pharmaceutical formulations suitable for injection or infusion may be in the form of a sterile aqueous solution, a dispersion or a sterile powder that contains the active ingredient, adjusted, if necessary, for preparation of such a sterile solution or dispersion suitable for infusion or injection. This may optionally be encapsulated into liposomes. In all cases, the final preparation must be sterile, liquid, and stable under production and storage conditions.

The liquid carrier or intermediate can be a solvent or liquid dispersive medium that contains, for example, water, ethanol, a polyol (e. g. glycerol, propylene glycol or the like), vegetable oils, non-toxic glycerine esters and suitable mixtures thereof. Suitable flowability may be maintained, by generation of liposomes, administration of a suitable particle size in the case of dispersions, or by the addition of surfactants. Prevention of the action of micro-organisms can be achieved by the addition of various antibacterial and antifungal agents, e. g. paraben, chlorobutanol, or sorbic acid. In many cases isotonic substances are recommended, e. g. sugars, buffers and sodium chloride to assure osmotic pressure similar to those of body fluids, particularly blood. Prolonged absorption of such injectable mixtures can be achieved by introduction of absorption-delaying agents, such as aluminium monostearate or gelatin.

Sterile injectable solutions can be prepared by mixing the new crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl) phenyl)propyl) thio)methyl) cyclopropane acetic acid with an appropriate solvent and one or more of the aforementioned excipients, followed by sterile filtering. In the case of sterile powders suitable for use in the preparation of sterile injectable solutions, preferable preparation methods include drying in vacuum and lyophilization, which provide powdery mixtures of the isostructural pseudopolymorphs and desired excipients for subsequent preparation of sterile solutions.

The compound of the present invention may also be used for the preparation of locally acting, topical formulations. Such formulations may also contain other pharmaceutically

acceptable excipients, such as polymers, oils, liquid carriers, surfactants, buffers, preservatives, stabilizers, antioxidants, moisturizers, emollients, colorants and odorants.

Examples of pharmaceutically acceptable polymers suitable for such topical formulations include, but are not limited to, acrylic polymers; cellulose derivatives, such as carboxymethylcellulose sodium, methylcellulose or hydroxypropylcellulose; natural polymers, such as alginates, tragacanth, pectin, xanthan and cytosan.

Examples of suitable pharmaceutically acceptable oils which are so useful include but are not limited to, mineral oils, silicone oils, fatty acids, alcohols, and glycols. Examples of suitable pharmaceutically acceptable liquid carriers include, but are not limited to, water, alcohols or glycols such as ethanol, isopropanol, propylene glycol, hexylene glycol, glycerol and polyethylene glycol, or mixtures thereof in which the new crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl) cyclopropane acetic acid is dissolved or dispersed, optionally with the addition of non-toxic anionic, cationic or non-ionic surfactants, and inorganic or organic buffers.

Suitable examples of pharmaceutically acceptable preservatives include, but are not limited to, various antibacterial and antifungal agents such as solvents, for example ethanol, propylene glycol, benzyl alcohol, chlorobutanol, quaternary ammonium salts, and parabens (such as methyl paraben, ethyl paraben, propyl paraben, etc.).

Suitable examples of pharmaceutically acceptable stabilizers and antioxidants include, but are not limited to, ethylenediaminetetraacetic acid (EDTA), thiourea, tocopherol and butyl hydroxyanisole.

Suitable examples of pharmaceutically acceptable moisturizers include, but are not limited to, glycerine, sorbitol, urea and polyethylene glycol.

Suitable examples of pharmaceutically acceptable emollients include, but are not limited to, mineral oils, isopropyl myristate, and isopropyl palmitate.

The use of dyes and odorants in topical formulations of the present invention depends on many factors of which the most important is organoleptic acceptability to the population that will be using the pharmaceutical formulations.

The therapeutically acceptable quantity of the new crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl) cyclopropane acetic acid of the present invention administered varies, dependent on the selected compound, the mode of administration, treatment conditions, age and status of the patient or animal species, and is subject to the final decision of the physician, clinician or veterinary doctor monitoring the course of treatment.

Suitable oral and parenteral doses may vary within the range of from about 14.5 to about 286 μg per kg of body weight per day, preferably from about 29 to about 214 μg per kg of body weight and more preferably from about 58 to about 143 μg per kg of body weight per day. The new crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl) cyclopropane acetic acid may be formulated in a single dosage form that contains from about 1 to about 20 mg, preferably from about 2 to about 15 mg, and more desirably from about 4 to about 10 mg of the active substance per unit dose.

Examples

The following Examples illustrate the invention, but are not limiting.

Example 1 - Preparation of the Crystalline Form

1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl) phenyl)propyl)thio) methyl)cyclopropane acetic acid (1 g) was suspended in acetone (100 ml) and citric buffer pH=5 (100 ml). The suspension was sonicated in an ultrasound bath at a temperature of 20 °C for 3 minutes. The precipitate formed after 24 h. The crystals were filtered off and dried at room temperature under atmospheric pressure to constant weight to give 0.85 g of the crystal form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio) methyl)cyclopropane acetic acid).

* * *

The present invention is not to be limited in scope by the specific embodiments described herein. Various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

All patents, applications, publications, test methods, literature, and other materials cited herein are hereby incorporated by reference.

WHAT IS CLAIMED IS:

1. Crystalline 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl)cyclopropane acetic acid having characteristic X-ray powder diffraction peaks, designated by 2θ and expressed in degrees, at 6.5±0.2°, 10.0±0.2°, 15.5±0.2°, 18.3±0.2°, 20.4±0.2° and 24.6±0.2°.

2. Crystalline 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl)cyclopropane acetic acid characterized by the monoclinic space group $P\,2_1$, and displaying unit cell parameters comprising:

crystal axis lengths of $a = 7.95(1)$ Å, $b = 21.94(1)$ Å, $c = 17.95(1)$ Å and

an angle between the crystal axes of $\beta = 100.03(1)°$.

3. A process for preparing the crystalline 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl)cyclopropane acetic acid of claim 1 or claim 2, comprising

(i) dissolving 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl)cyclopropane acetic acid, or a salt thereof, in a mixture of acetone and one or more aqueous buffers, and

(ii) recrystallizing the 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl)cyclopropane acetic acid.

4. The process of claim 3, wherein the ratio of one or more aqueous buffers to acetone is from about 1:5 to about 5:1.

5. The process of claim 3, wherein the crystallization step is performed at a pH of about 5 to about 8.

6. The process of claim 3, wherein recrystallization is performed at a temperature of from about 5 °C to about 50 °C.

7. The process of claim 3, further comprising

(iii) isolating the crystalline 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl)cyclopropane acetic acid.

8. Crystalline 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl)cyclopropane acetic acid prepared by the process of claim 3.

9. The crystalline 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl)cyclopropane acetic acid of claim 1 or claim 2, having a purity of greater than about 90.0%.

10. The crystalline 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl)cyclopropane acetic acid of claim 1 or claim 2, having a purity of greater than about 95.0%.

11. The crystalline 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl)cyclopropane acetic acid of claim 1 or claim 2, having a purity of greater than about 99.0%.

12. The crystalline 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl)cyclopropane acetic acid of claim 1 or claim 2, having a purity of greater than about 99.9%.

13. A pharmaceutical composition comprising the crystalline 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio) methyl) cyclopropane acetic acid according to claim 1 or claim 2, and one or more pharmaceutically acceptable carriers or excipients.

14. A method of treating asthma in a human which comprises administering to a patient in need of such treatment an effective amount of the crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl) propyl)thio)methyl) cyclopropane acetic acid of claim 1 or claim 2.

ABSTRACT

The present invention relates to a new crystalline form of 1-(((1(*R*)-(3-(2-(7-chloro-2-quinolinyl)ethenyl)-phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl) cyclopropane acetic acid, to a process for its preparation, to pharmaceutical formulations containing it, and to a method of treatment using the same

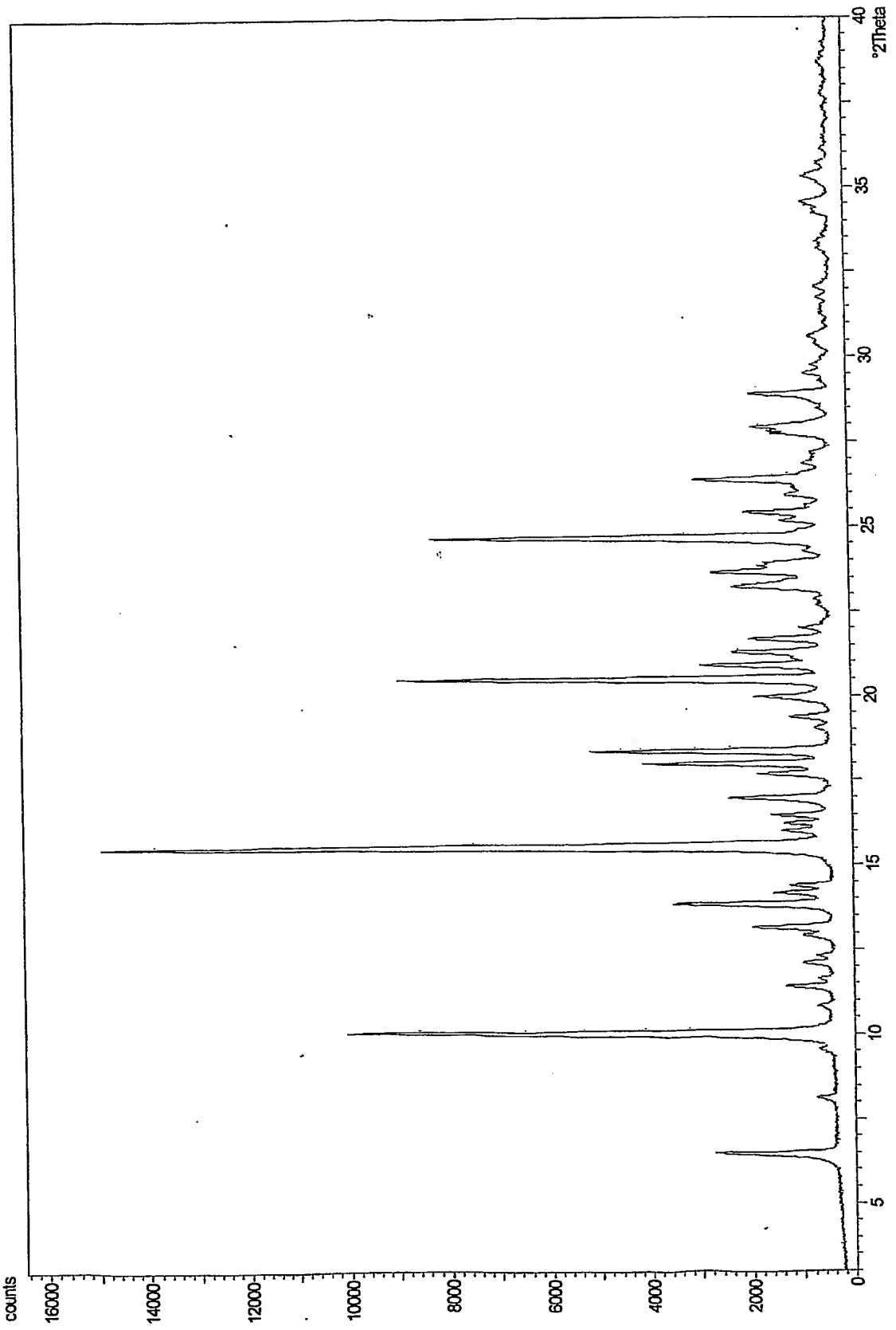

Figure 1.

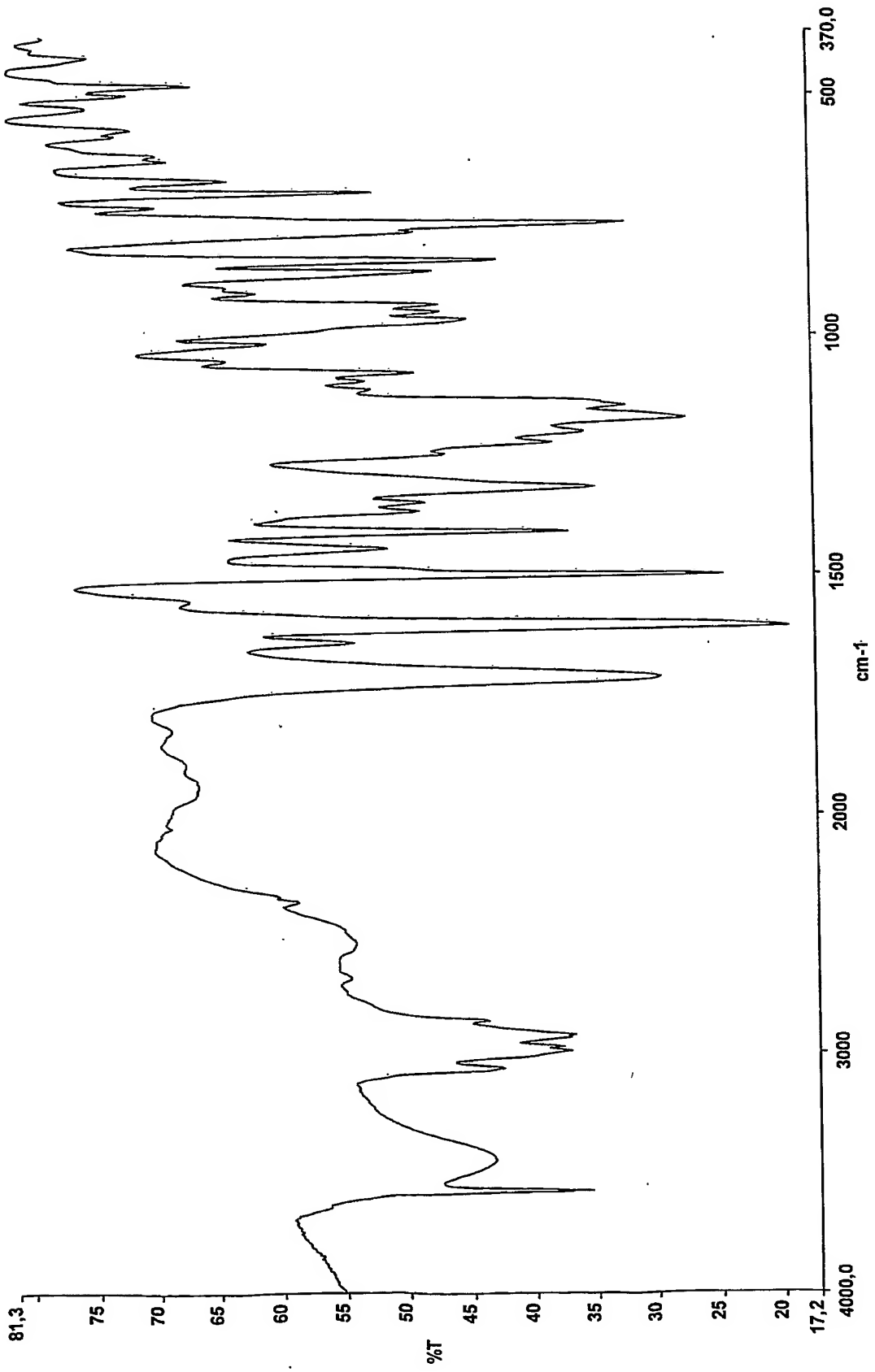

Figure 2.

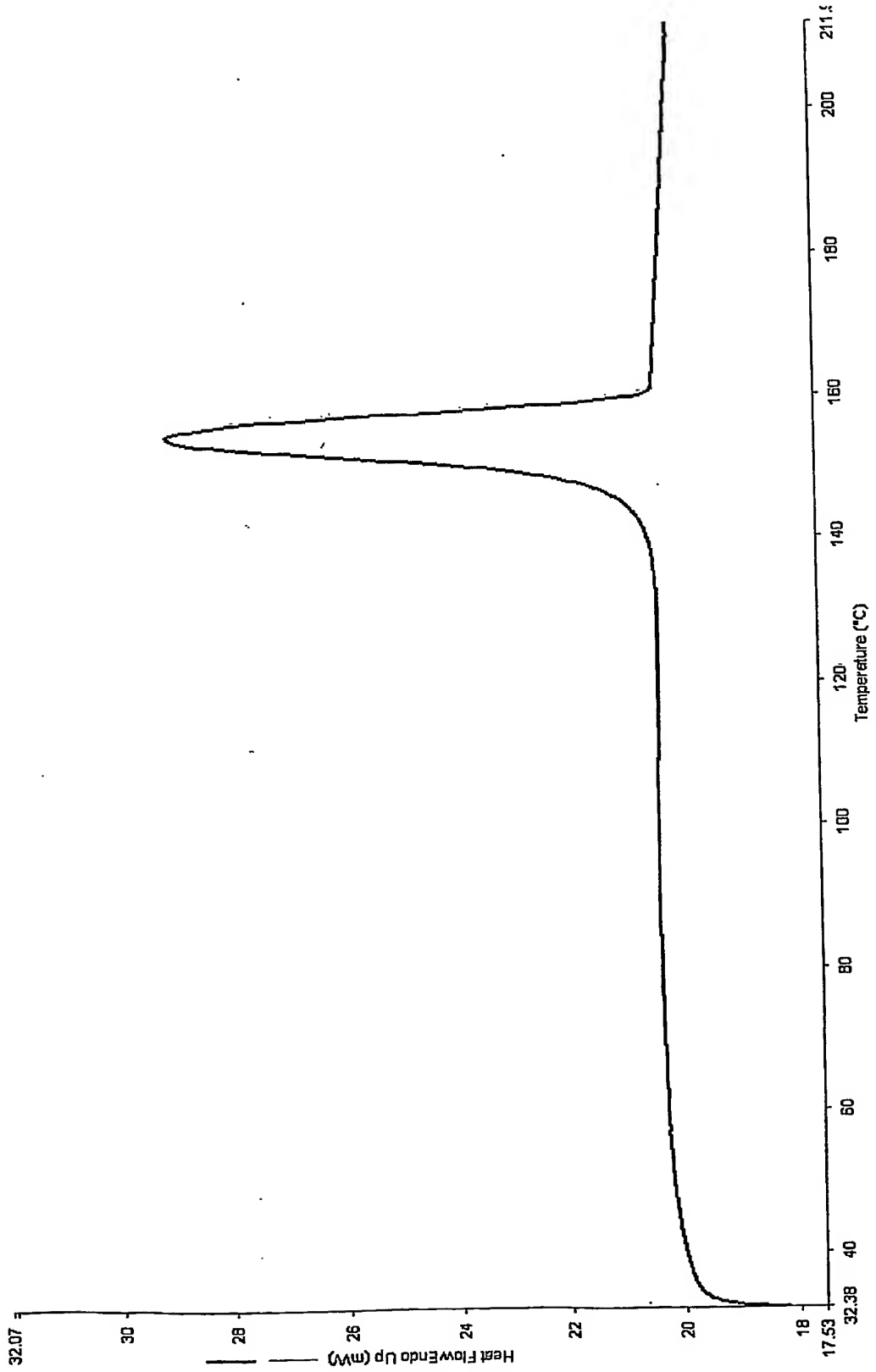

Figure 3.